CLAIMS

1. A method for assessing the potential of a compound to function as an anti-arrhythmic agent comprising:
(a) providing a cell that expresses a recombinant mutant Nav1 sodium channel protein;
(b) measuring a first plateau current in said cell;
(c) exposing said cell to a test compound;
(d) measuring a second plateau current in said cell; and
(e) comparing said first and second currents whereby a lower second current indicates that said test compound is a potential anti-arrhythmic agent;
said mutant sodium channel protein having an amino acid sequence in which one or more amino acids among the ten amino acids occurring at the carboxy end of the S6 segments of D1, D2, D3 or D4 domains of a mammalian Nav1 protein differs from the amino acid in wild-type Nav1 by substitution with tryptophan, phenylalanine, tyrosine or cysteine.

2. The method of claim 1 wherein said mammalian Nav 1 protein is selected from Nav 1.1, Nav 1.2, Nav 1.3, Nav 1.4, Nav 1.5, Nav 1.6, Nav 1.7, or Nav 1.8.

3. The method of claim 2 wherein said mammalian Nav 1 protein is Nav 1.4 or Nav 1.5.

4. A method for assessing the potential of a compound as an anti-arrhythmic agent comprising:
(a) providing a cell that expresses a recombinant mutant Nav1 sodium channel protein;
(b) measuring a first plateau current in said cell;
(c) exposing said cell to a test compound;
(d) measuring a second plateau current in said cell; and

(e) comparing said first and second currents whereby a lower second current indicates that said test compound is a potential anti-arrhythmic agent;
said mutant sodium channel protein having an amino acid sequence in which at least one amino acid chosen from amino acids 19, 21 and 22 of the S6 segment of D1 and amino acids 23 and 24 of the S6 segment of the D4 domain of a mammalian Nav1 protein differs from the amino acid in wild-type Nav1 by substitution with tryptophan, phenylalanine, tyrosine or cysteine.

5. The method of claim 4 wherein said mammalian Nav 1 protein is selected from Nav 1.1, Nav 1.2, Nav 1.3, Nav 1.4, Nav 1.5, Nav 1.6, Nav 1.7, or Nav 1.8.

6. The method of claim 5 wherein said mammalian Nav 1 protein is Nav 1.4 or Nav 1.5.

7. A method for assessing the potential of a compound as an anti-arrhythmic agent comprising:
(a) providing a human cell that expresses a recombinant mutant Nav1.4 or Nav1.5 sodium channel protein;
(b) measuring a first plateau current in said cell;
(c) exposing said cell to a test compound;
(d) measuring a second plateau current in said cell; and
(e) comparing said first and second currents whereby a lower second current indicates that said test compound is a potential anti-arrhythmic agent;
said mutant sodium channel protein having an amino acid sequence in which at least one amino acid chosen from amino acids L435, L437, A438, I1589 and I1590 of wild-type rNav1.4 is replaced by tryptophan, phenylalanine or tyrosine, or in the case of L437 additionally with cysteine.

8. A method according to claim 1 wherein said cell is chosen from a human embryonic kidney cell and a Chinese hamster ovary cell.

9. A method according to claim 1 wherein one or more wild-type amino acids are replaced with tryptophan.

10. A method according to claim 3 wherein the mammalian Nav1.4 or Nav1.5 is rat or human Nav1.4 or Nav1.5 and a leucine corresponding to L437 of rNav1.4 is replaced with cysteine.

11. A method according to claim 10 wherein L437 is replaced with cysteine and one or both of a leucine and an alanine corresponding to L435 and A438 respectively of rNav1.4 are replaced with tryptophan.

12. The method according to claim 3 wherein the mammalian Nav1.4 or Nav1.5 is rat or human Nav1.4 or Nav1.5.

13. The method according to claim 12 wherein an alanine corresponding to A438 and an isoleucine corresponding to I1589 in rNav1.4 are replaced.

14. The method according to claim 13 wherein said alanine and isoleucine are replaced by tryptophan.

15. A cell comprising a nucleic acid that encodes a recombinant mutant mammalian Nav1 protein, said mutant protein having a sequence in which one or more amino acids among the ten amino acids occurring at the carboxy end of the S6 segments of D1, D2, D3 or D4 domains of mammalian Nav1 differs from the amino acid in wild-type Nav1 by substitution with tryptophan, phenylalanine, tyrosine or cysteine.

16. The cell of claim 15 wherein said mammalian Nav 1 protein is selected from Nav 1.1, Nav 1.2, Nav 1.3, Nav 1.4, Nav 1.5, Nav 1.6, Nav 1.7, Nav 1.8, or Nav 1.9.

17. The cell of claim 16 wherein said mammalian Nav 1 protein is Nav 1.4 or Nav 1.5.

18. A cell comprising a nucleic acid that encodes a recombinant mutant mammalian Navl protein, said mutant protein having an amino acid sequence in which at least one amino acid chosen from amino acids 19, 21 and 22 of the S6 segment of D1 and amino acids 23 and 24 of the S6 segment of the D4 domain of mammalian Navl differs from the amino acid in wild-type Navl by substitution with tryptophan, phenylalanine, tyrosine or cysteine.

19. The cell of claim 18 wherein said mammalian Nav 1 protein is selected from Nav 1.1, Nav 1.2, Nav 1.3, Nav 1.4, Nav 1.5, Nav 1.6, Nav 1.7, Nav 1.8, or Nav 1.9.

20. The cell of claim 19 wherein said mammalian Nav 1 protein is Nav 1.4 or Nav 1.5.

21. A human cell comprising a nucleic acid that encodes a mutant mammalian Navl.4 or Navl.5 protein, said mutant sodium channel protein having an amino acid sequence in which at least one amino acid chosen from amino acids L435, L437, A438, I1589 and I1590 of wild-type rat Navl.4 is replaced by tryptophan, phenylalanine or tyrosine, or in the case of L437 additionally with cysteine.

22. A cell according of claim 15 wherein said mutant sodium channel protein gives rise to sodium channels exhibiting plateau currents of greater than 1 nanoamp.

23. An isolated nucleic acid comprising a nucleotide sequence that codes for a mutant mammalian Navl protein, said mutant protein having an amino acid sequence in which one or more amino acids among the ten amino acids occurring at the carboxy end of the S6 segments of D1, D2, D3 or D4 domains of

mammalian Nav1 differs from the amino acid in wild-type Nav1 by substitution with tryptophan, phenylalanine, tyrosine or cysteine.

24. The isolated nucleic acid of claim 23 wherein said mammalian Nav 1 protein is selected from Nav 1.1, Nav 1.2, Nav 1.3, Nav 1.4, Nav 1.5, Nav 1.6, Nav 1.7, Nav 1.8 or Nav 1.9.

25. The isolated nucleic acid of claim 24 wherein said mammalian Nav 1 protein is Nav 1.4 or Nav 1.5.

26. An isolated nucleic acid comprising a nucleotide sequence that codes for a mutant mammalian Nav1.4 or Nav1.5 protein, said mutant protein having an amino acid sequence in which at least one amino acid chosen from amino acids 19, 21 and 22 of the S6 segment of D1 and amino acids 23 and 24 of the S6 segment of the D4 domain of said mutant mammalian Nav1.4 or Nav1.5 differs from the amino acid in wild-type mammalian Nav1.4 or Nav1.5 by substitution with tryptophan, phenylalanine, tyrosine or cysteine.

27. An isolated nucleic acid comprising a nucleotide sequence that codes for a rat or human Nav1.4 or Nav1.5 protein in which one or more amino acids corresponding to wild-type amino acids L435, L437, A438, I1589 and I1590 of rNav1.4 is replaced with tryptophan, phenylalanine or tyrosine, or in the case of L437 additionally with cysteine.

28. A isolated functional sodium channel protein comprising a first amino acid sequence chosen from:

WILAVVAMAY	SEQ ID NO.: 36
YILAVVAMAY	SEQ ID NO.: 37
FILAVVAMAY	SEQ ID NO.: 38
LILWVVAMAY	SEQ ID NO.: 39

LILYVVAMAY	SEQ ID NO.: 40
LILFVVAMAY	SEQ ID NO.: 41
LICWVVAMAY	SEQ ID NO.: 42
LICYVVAMAY	SEQ ID NO.: 43
LICFVVAMAY	SEQ ID NO.: 44
WICWVVAMAY	SEQ ID NO.: 45
YICYVVAMAY	SEQ ID NO.: 46
FICFVVAMAY	SEQ ID NO.: 47
WICYVVAMAY	SEQ ID NO.: 48
WICFVVAMAY	SEQ ID NO.: 49
YICWVVAMAY	SEQ ID NO.: 50
FICWVVAMAY	SEQ ID NO.: 51
YICYVVAMAY	SEQ ID NO.: 52
FICFVVAMAY	SEQ ID NO.: 53
YICFVVAMAY	SEQ ID NO.: 54
FICYVVAMAY	SEQ ID NO.: 55
LIWAVWAMAY	SEQ ID NO.: 56
LIYAVWAMAY	SEQ ID NO.: 57
LIFAVWAMAY	SEQ ID NO.: 58
LILAVWAMAY	SEQ ID NO.: 59
MYIAWILENF	SEQ ID NO.: 60
MYIAYILENF	SEQ ID NO.: 61
MYIAFILENF	SEQ ID NO.: 62
MYIAIWLENF	SEQ ID NO.: 63
MYIAIYLENF	SEQ ID NO.: 64
MYIAIFLENF	SEQ ID NO.: 65
MYIACILENF	SEQ ID NO.: 66
MYIAICLENF	SEQ ID NO.: 67
MYIAWWLENF	SEQ ID NO.: 68
MYIAYYLENF	SEQ ID NO.: 69

MYIAFFLENF	SEQ ID NO.: 70

29. A functional sodium channel protein comprising first and second amino acid sequences, said first amino acid sequence chosen from:

WILAVVAMAY SEQ ID NO.: 36
LILWVVAMAY SEQ ID NO.: 39
LICWVVAMAY SEQ ID NO.: 42
WICWVVAMAY SEQ ID NO.: 45, and
LILAVWAMAY SEQ ID NO.: 59

and said second amino acid sequence chosen from:

MYIAWILENF SEQ ID NO.: 60
MYIAIWLENF SEQ ID NO.: 63
MYIACILENF SEQ ID NO.: 66
MYIAICLENF SEQ ID NO.: 67, and
MYIAWWLENF SEQ ID NO.: 68.

30. A functional recombinant sodium channel protein according to claim 18 additionally comprising a second amino acid sequence YMIFFX^{a}X^{b}X^{c}IFLGSFYLX^{d}N (SEQ ID NO. 71) immediately adjacent and amino-terminal to said first amino acid sequence, wherein X^a is chosen from V and M; X^b is chosen from L and V; X^c is chosen from I and V; and X^d is chosen from I and V.

31. A screen for assessing the potential of a compound to treat a pathological condition manifested by an increased late sodium current in a heart comprising:
(a) providing a cell that expresses a recombinant mutant Nav1 sodium channel protein;
(b) measuring a first plateau current in said cell;
(c) exposing said cell to a test compound;
(d) measuring a second plateau current in said cell; and

(e) comparing said first and second currents whereby a lower second current indicates that said test compound is a potential anti-arrhythmic agent;
said mutant sodium channel protein having an amino acid sequence in which one or more amino acids among the ten amino acids occurring at the carboxy end of the S6 segments of D1, D2, D3 or D4 domains of mammalian Navl differs from the amino acid in wild-type Navl by substitution with tryptophan, phenylalanine, tyrosine or cysteine.

32. The method of claim 31 wherein said mammalian Navl protein is selected from Nav 1.1, Nav 1.2, Nav 1.3, Nav 1.4, Nav 1.5, Nav 1.6, Nav 1.7, or Nav 1.8.

33. The method of claim 32 wherein said mammalian Nav 1 protein is Nav 1.4 or Nav 1.5.

34. A screen for assessing the potential of a compound to treat a pathological condition manifested by an increased late sodium current in a heart comprising:
(a) providing a cell that expresses a mutant Navl sodium channel protein;
(b) measuring a first plateau current in said cell;
(c) exposing said cell to a test compound;
(d) measuring a second plateau current in said cell; and
(e) comparing said first and second currents whereby a lower second current indicates that said test compound is a potential anti-arrhythmic agent;
said mutant sodium channel protein having an amino acid sequence in which at least one amino acid chosen from amino acids 19, 21 and 22 of the S6 segment of D1 and amino acids 23 and 24 of the S6 segment of the D4 domain of mammalian Navl.4 or Navl.5 differs from the amino acid in wild-type Navl by substitution with tryptophan, phenylalanine, tyrosine or cysteine.

35. The method of claim 34 wherein said mammalian Navl protein is selected from Nav 1.1, Nav 1.2, Nav 1.3, Nav 1.4, Nav 1.5, Nav 1.6, Nav 1.7, or Nav 1.8.

36. The method of claim 35 wherein said mammalian Nav 1 protein is Nav 1.4 or Nav 1.5.

37. A screen for assessing the potential of a compound to treat a pathological condition manifested by an increased late sodium current in a heart comprising:
(a) culturing a human cell that produces mutant Nav1.4 or Nav1.5 sodium channel protein;
(b) measuring a first plateau current in said cell;
(c) exposing said cell to a test compound;
(d) measuring a second plateau current in said cell; and
(e) comparing said first and second currents whereby a lower second current indicates that said test compound is a potential anti-arrhythmic agent;
said mutant sodium channel protein having an amino acid sequence in which at least one amino acid chosen from amino acids L435, L437, A438, I1589 and I1590 of wild-type rNav1.4 is replaced by tryptophan, phenylalanine or tyrosine, or in the case of L437 additionally with cysteine.

38. A screen according to claim 34 wherein said cell is chosen from a human embryonic kidney cell and a Chinese hamster ovary cell.

39. A screen according to claim 34 wherein one or more wild-type amino acids are replaced with tryptophan.

40. A screen according to claim 34 wherein the mammalian Nav1.4 or Nav1.5 is rat or human Nav1.4 or Nav1.5 and a leucine corresponding to L437 of rNav1.4 is replaced with cysteine.

41. A screen according to claim 40 wherein L437 is replaced with cysteine and one or both of a leucine and an alanine corresponding to L435 and A438 respectively of rNav1.4 are replaced with tryptophan.

42. A screen according to claim 34 wherein the mammalian Nav1.4 or Nav1.5 is rat or human Nav1.4 or Nav1.5.

43. A screen according to claim 42 wherein an alanine corresponding to A438 and an isoleucine corresponding to I1589 in rNav1.4 are replaced.

44. A screen according to claim 43 wherein said alanine and isoleucine are replaced by tryptophan.

45. A screen according to claim 34 wherein said mutant sodium channel protein gives rise to sodium channels exhibiting plateau currents of greater than 1 nanoamp.